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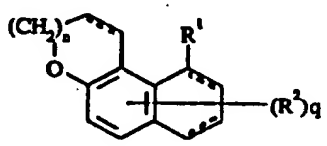

(I)

(57) Abstract

A compound of formula (I) and pharmaceutically acceptable salts and solvates thereof, wherein R^1 is a group of the formula - $CR^3R^4(CH_2)pNR^5COR^6$; R^2 is hydrogen, halogen, C_{1-6}alkyl, OR^7 or CO_2R^7, and may be the same or different substituent when q is 2; R^3, R^4 and R^5, which may be the same or different, are hydrogen or C_{1-6}alkyl; R^6 is C_{1-6}alkyl or C_{3-7}cycloalkyl; R^7 is hydrogen or C_{1-6}alkyl; n is zero, 1 or 2; p is an integer of 1, 2, 3 or 4; q is 1 or 2; and the dotted lines indicate the absence or presence of an additional bond.

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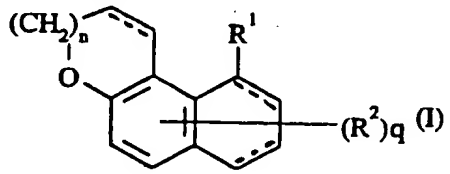
NAPHTHALENE DERIVATIVES, METHOD OF PREPARATION AND USE

This invention relates to tricyclic naphthalene derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to their medical use.

The invention thus provides compounds of formula (I)



and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof, wherein R^1 is a group of the formula $-CR^3R^4(CH_2)pNR^5COR^6$;

R^2 is hydrogen, halogen, C_{1-6}alkyl, OR^7 or CO_2R^7, and may be the same or different substituent when q is 2;

R^3, R^4 and R^5, which may be the same or different, are hydrogen or C_{1-6}alkyl;

R^6 is C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^7 is hydrogen or C_{1-6}alkyl;

n is zero, 1 or 2;

p is an integer of 1, 2, 3 or 4;

q is 1 or 2; and

the dotted lines indicate the absence or presence of an additional bond.

It will be appreciated that in formula (I) hereinabove the substituent R^2 may be attached at any available position on the carbocyclic portion of the tricylic ring other than the position occupied by the R^1 group.

As used herein, an alkyl group may be a straight chain or branched chain alkyl group. Examples of suitable alkyl groups include C_{1-4} alkyl groups, for example methyl, ethyl and isopropyl groups. A preferred alkyl group is methyl.

A halogen substituent may be, for example, fluorine, chlorine, bromine or iodine.

R^1 preferably represents a group $-CR^3R^4(CH_2)_pNHCOR^6$ wherein R^3 and R^4 each independently represent hydrogen or C_{1-3} alkyl, especially hydrogen, p is an integer of 1 or 2, especially 1, and R^6 is C_{1-3} alkyl (e.g. methyl) or C_{3-5} cycloalkyl (e.g. cyclopropyl or cyclobutyl).

Examples of the group R^2 include hydrogen, halogen (e.g. fluorine) and C_{1-3} alkyl (e.g. methyl). Particular examples of R^2 are hydrogen or halogen.

Aptly, n is zero or 1.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Specific compounds according to the invention include:

N-(2-naphtho[2,1-b]furan-9-yl-ethyl)-acetamide
N-[2-(1,2,6,7,8,9-hexahydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide
N-[2-(1,2-dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide
N-[2-(4-fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide
N-[2-(4-fluoro-1,2-dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide
N-[2-(2,3-dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide
N-[2-(3H-benzo[f]chromen-10-yl)-ethyl]-acetamide
N-[2-(5-fluoro-2,3-dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide
Cyclopropanecarboxylic acid[2-(4-fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]-amide
N-[2-(5-Fluoro-3H-benzo[f]chromen-10-yl)-ethyl-acetamide;

and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

A particularly suitable compound according to the present invention is N-[2-(1,2-dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide, and pharmaceutically acceptable salts and solvates thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. A particularly suitable pharmaceutically acceptable salt of the compounds of formula (I) is the hydrochloride salt. Other acids such as oxalic, while not, in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

References hereinafter to a compound of formula (I) includes the compound and its pharmaceutically acceptable salts.

The compounds of formula (I) may contain at least one asymmetric carbon atom and may exist as stereoisomers. The compounds of formula (I) thus include the d- and l-isomers and mixtures, for example racemic mixtures, thereof.

The compounds of formula (I) have a high affinity and selectivity for binding to melatonin receptors as demonstrated in chick retinal membranes according to the method of Dubocovich ML, FASEB J, 2, 2765-2773 (1988) and have either melatonin agonist or antagonist activity. Accordingly, the compounds are of use as scientific tools for studying the role of melatonin within biological systems.

The compounds of formula (I) are also of use in the treatment of disorders which arise from a disturbed functioning of the melatonin system. In particular the compounds of formula (I) may be used in the treatment of chronobiological disorders, especially in the elderly population, glaucoma, cancer, psychiatric disorders, neurodegenerative diseases or neuroendocrine disorders arising as a result of or influenced by the melatonin system.

Chronobiological disorders include seasonal affective disorders (SAD), primary and secondary insomnia disorders, primary and secondary hypersomnia disorders, sleep-wake schedule disorders (including advanced phase type, delayed phase type, disorganised type and frequently-changing type) and other dyssomnias, especially those caused by ageing, dementias, blindness, shift work and by rapid time-zone travel, commonly known as jet lag.

Cancers which may be treated with a compound of formula (I) include solid tumours, e.g. melanomas and breast carcinomas.

Psychiatric disorders which may be related to altered melatonin function or influenced by melatonin and circadian rhythms include mood disorders (including bipolar disorders of all types, major depression, dysthymia and other depressive disorders), psychoactive substance dependence and abuse, anxiety disorders (including panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder, post-traumatic stress disorder and generalised anxiety disorder), schizophrenia, epilepsy and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures), disorders of involuntary movement (including those due to Parkinson's disease, and drug-induced involuntary movements) and dementias (including primary degenerative dementia of the Alzheimer type).

Neurodegenerative diseases which may be related to altered melatonin function or influenced by melatonin and biological rhythms include multiple sclerosis and stroke.

Neuroendocrine disorders which may be related to altered melatonin function or influenced by melatonin and biological rhythms include peptic

ulceration, emesis, psoriasis, benign prostatic hyperplasia, hair condition and body weight. Particular neuroendocrine disorders which may be treated include those relating to the regulation of reproductive maturation and function include idiopathic delayed puberty, sudden infant death, premature labour, infertility, antifertility, premenstrual syndrome (including late luteal phase dysphoric disorder) and sexual dysfunction (including sexual desire disorders, male erectile disorder, post-menopausal disorders and orgasm disorders). The compounds may also be used to manipulate breeding cycles, body weight, coat colour and oviposition of susceptible hosts, including birds, insects and mammals. The compounds of formula (I) may also have sedative and analgesic effects, effects on the microcirculation and immunomodulant effects and may be useful for the treatment of hypertension, migraine, cluster headache, regulation of appetite and in the treatment of eating disorders such as obesity, anorexia nervosa and bulimia nervosa.

There is thus provided in a further aspect of the invention a compound of formula (I) for use in therapy, in particular in human medicine. It will be appreciated that use in therapy embraces but is not necessarily limited to use of a compound of formula (I) as an active therapeutic substance.

There is also provided as another aspect of the invention a compound of formula (I) for use in the preparation of a medicament for use in the treatment of conditions associated with a disturbed functioning of the melatonin system.

In an alternative or further aspect of the invention there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I), in particular for the treatment of conditions associated with a disturbed functioning of the melatonin system.

It will be appreciated by those skilled in the art that reference herein to therapy and treatment extends to prophylaxis as well as the treatment of established symptoms.

While it is possible that, for use in therapy, a compound of formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor. The carrier(s) must be 'acceptable' in the sense of

being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

There is also provided by the present invention a process of preparing a pharmaceutical formulation, which process comprises mixing a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor.

Pharmaceutical formulations include those suitable for oral, rectal, vaginal, nasal, topical or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch, crosscarmellose sodium or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For topical administration in the mouth, the compositions may take the form of buccal or sub-lingual tablets, drops or lozenges formulated in conventional manner.

For topical administration to the epidermis the compounds may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable dissolving, thickening, gelling, emulsifying, stabilising, dispersing, suspending and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Pessaries for vaginal administration may be formulated in a similar manner.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser. In the case of a pressurised aerosol, the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, carbon dioxide or other suitable gas is required. The composition may take such forms as suspensions, solutions or emulsions, and may contain formulatory agents, such as surfactants, e.g. oleic acid or lecithins. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Formulations for nebulisation may be presented in unit dosage form, e.g. in ampoules or vials, taking such form as solutions or suspensions, and may contain formulatory agents, such as suspending and stabilising agents. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may

be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Any of the pharmaceutical compositions described above may be presented in a conventional manner associated with controlled release forms, such as compression coated tablets.

The active ingredient may conveniently be presented in unit dose form. A convenient unit dose formulation contains the active ingredient in an amount of from about 0.1mg to about 200mg.

It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular compound used and the frequency and route of administration and will ultimately be at the discretion of the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

A proposed dose of the compounds of the invention for oral, rectal, vaginal, intranasal, topical or parenteral administration to man (of approximately 70kg bodyweight) for the treatment of conditions associated with a disturbed functioning of the melatonin system is 0.01 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

For oral administration a unit dose will preferably contain from 0.1 to 200mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 5 mg of the active ingredient.

Pressurised aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised pack contains 0.2 mg to 2 mg of a compound of the invention, and capsules and cartridges delivered from an insufflator or an inhaler or each unit dose for nebulisation, contain 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation with an aerosol will be within the range 1 mg to 100 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

Dosages of the compounds of the invention for rectal, vaginal, intranasal or topical administration are similar to those for oral administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents such as a hypnotic or

antidepressant agent, or an anti-cancer agent such as tamoxiphen, or in combination with radiation therapy to treat cancer.

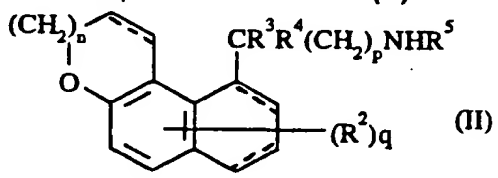
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a compound of formula (I) together with at least one other therapeutic agent and one or more pharmaceutically acceptable carriers therefor comprise a further aspect of the invention.

When compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

When such combinations are employed the dose of each component of the combination will in general be that employed for each component when used alone.

Compounds of formula (I) and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof, may be prepared by methods known in the art for the preparation of analogous compounds. In particular the compounds of formula (I) may be prepared by the methods outlined below and which form a further aspect of the invention. In the following processes, R^1 to R^7, n, p and q are as defined for formula (I) unless stated otherwise.

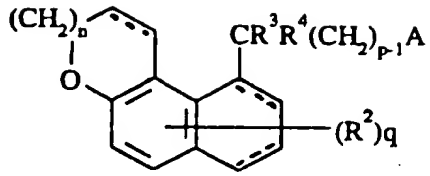
According to one general process (A) a compound of formula (I) may be prepared by acylation of a compound of formula (II)



(II)

Suitable acylating agents which may conveniently be used in the above process include acid anhydrides and acid halides. The reaction is conveniently effected in a suitable solvent such as an ether (e.g. diethyl ether, tetrahydrofuran or dioxan), a hydrocarbon such as toluene or a halogenated hydrocarbon (e.g. dichloromethane), preferably in the presence of a base such as pyridine or a tertiary amine (e.g. diisopropylethylamine), at a temperature in the range of 0 to 100^0C, preferably 0 to 20^0C.

A compound of formula (II) in which R^5 is hydrogen may conveniently be prepared by the reduction of a compound of formula (III)

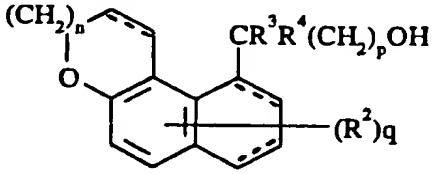


(III)

(wherein A is -CN or $-CONH_2$). The reduction may conveniently be effected using a boron hydride reducing agent such as borane-tetrahydrofuran complex in an ether solvent (e.g. tetrahydrofuran) at a suitable temperature, for example from 0° to 100°C.

Compounds of formula (II) in which R^5 is C_{1-6} alkyl may be prepared by N-alkylation of compounds of formula (II) in which R^5 is hydrogen using standard procedures.

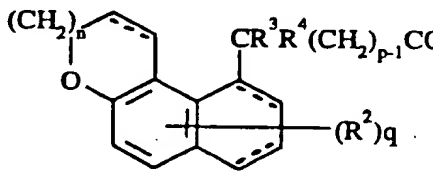
A compound of formula (II) in which R^5 is hydrogen may also be prepared from a compound of formula (IV)



(IV)

by treating said compound of formula (IV) with phthalimide in the presence of triphenylphosphine and a dialkylazodicarboxylate in a suitable solvent such as an ether (e.g. tetrahydrofuran) at about ambient temperature, and then heating the so-formed phthalimido compound with hydrazine hydrate in an alcoholic solvent (e.g. ethanol or aqueous ethanol) at reflux until the reaction to provide the desired compound of formula (II) is complete.

A compound of formula (III) in which A represents $-CONH_2$ may conveniently be prepared by reacting a corresponding carboxylic acid of formula (V)

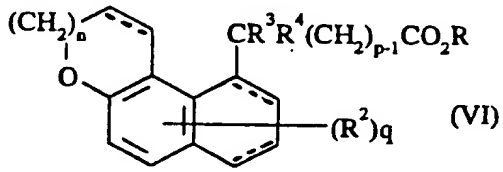


(V)

with ammonia solution in the presence of a coupling agent such as N,N'-carbonyldiimidazole or dicyclohexylcarbodiimide or other suitable coupling agent known in the art, for example from peptide synthesis. The coupling agent is first added to a compound of formula (V) in a suitable solvent such as an ether (e.g. tetrahydrofuran) and the mixture then treated with the ammonia

solution. The reaction may conveniently be carried out at about ambient temperature.

A compound of formula (V) may conveniently be prepared by the saponification of a compound of formula (VI)

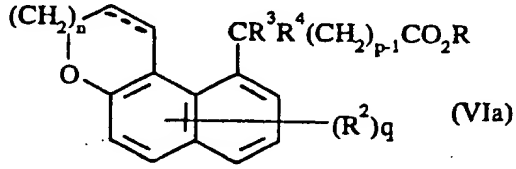


(VI)

(where R is an alkyl group such as methyl). The hydrolysis may be carried out in the presence of a suitable base such as an alkali metal hydroxide (e.g. lithium hydroxide) in a suitable solvent such as water, an ether (e.g. tetrahydrofuran) or an alcohol (e.g. methanol or ethanol) or a mixture thereof. The reaction may conveniently be carried out at about ambient temperature.

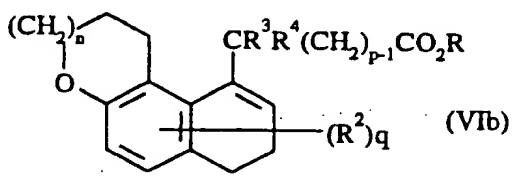
A compound of formula (VI) in which R is a lower alkyl group such as methyl may also be reduced to a corresponding compound of formula (IV). The reduction may conveniently be carried out by treating a compound of formula (VI) with a suitable reducing agent such as a hydride reducing agent (e.g. lithium borohydride or lithium aluminium hydride) in a suitable solvent such as an ether (e.g. tetrahydrofuran or diethyl ether or a mixture thereof) conveniently at about ambient temperature.

A compound of formula (VI) in which one or more of the dotted lines indicates an additional bond may conveniently be prepared by oxidising an appropriately saturated compound of formula (VI). Thus, for example, a compound of formula (VIa)



(VIa)

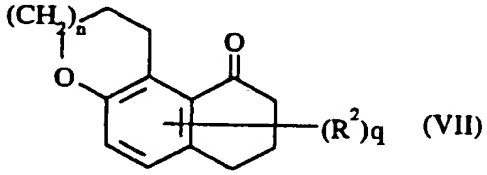
may conveniently be prepared by oxidising a partially saturated compound of formula (VIb)



(VIb)

The oxidation may be carried out by refluxing the partially saturated compound of formula (VIb) with p-chloranil in xylenes, alternatively palladium on carbon in p-cymene may be employed.

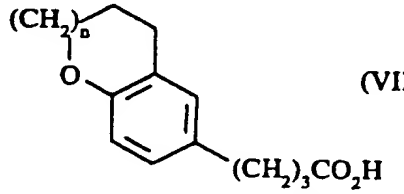
A compound of formula (VIb) may be prepared by treating a compound of formula (VII)



(VII)

with zinc, iodine and a compound $HalCR^3R^4(CH_2)_{p-1}CO_2R$ (where Hal is a halogen atom, e.g. bromine) in a suitable solvent such as toluene or an ether (e.g. diethyl ether) or a mixture of these solvents under reflux, followed by the addition of a suitable acid such as p-toluenesulphonic acid.

A compound of formula (VII) in which R^2 is hydrogen may be prepared by cyclising a compound of formula (VIII)



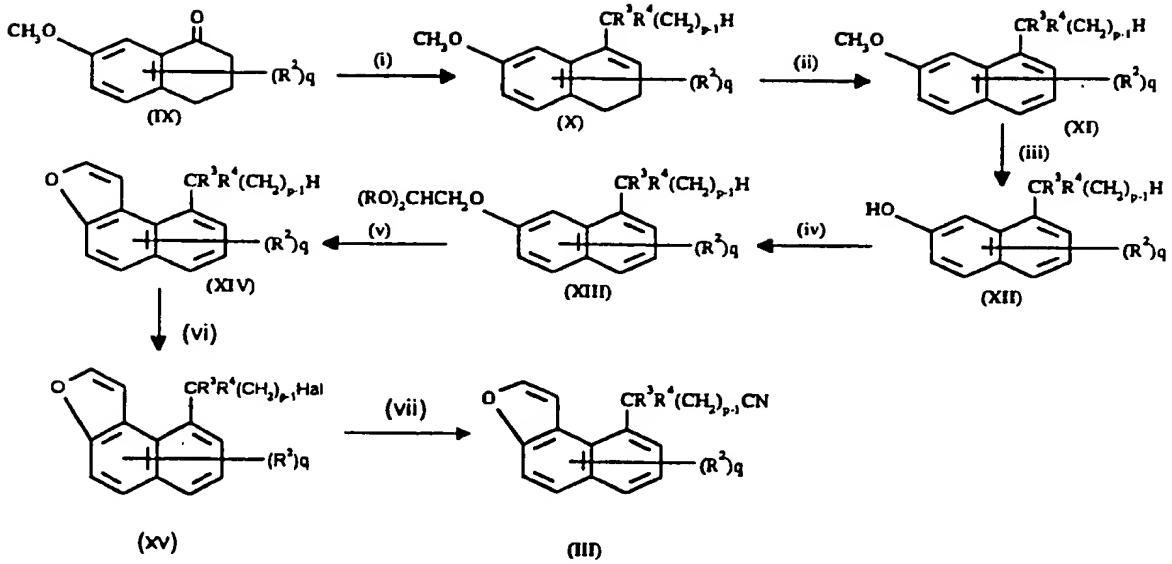
(VIII)

The cyclisation may conveniently be effected by converting the acid of formula (VIII) to an activated derivative such as the corresponding acid chloride, for example using thionyl chloride as the chlorinating agent, and then treating the acid chloride with $SnCl_4$ in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane) at about ambient temperature. A compound of formula (VII) in which R^2 is other than hydrogen may be similarly prepared from an appropriately substituted compound of formula (VIII).

Compounds of formula (VIII) are either known in the art (cf. Bull. Soc. Chim. France (1955), 931) or may be prepared by methods analogous to those described in the art for preparing the known compounds of formula (VIII).

A fully unsaturated compound of formula (III) in which A represents -CN, n is zero and p is 1 may conveniently be prepared according to Scheme 1 hereinafter

Scheme 1



Step (i) comprises treating a compound of formula (IX) with an alkylcerium (III) halide such as methylcerium (III) chloride (conveniently freshly prepared from cerium (III) chloride and methyllithium) in an ether solvent (e.g. tetrahydrofuran) at a low temperature (e.g. -78°C) and then completing the reaction at ambient temperature.

Step (ii) comprises oxidising (X) with p-chloranil in xylenes under reflux.

Step (iii) comprises treating (XI) with boron tribromide in a halogenated hydrocarbon solvent followed by the addition of a suitable acid such as hydrochloric acid at a temperature of from about 0°C to about 20°C.

Step (iv) comprises a conventional alkylation reaction with an alkylating agent $(RO)_2CHCH_2Hal$ (where Hal is a halogen atom, e.g. bromine, and R is a lower alkyl group, e.g. ethyl).

Step (v) comprises treating the acetal (XIII) with a suitable acid (e.g. polyphosphoric acid) in a solvent such as toluene and completing the reaction by maintaining the mixture at reflux.

Step (vi) comprises halogenation, typically bromination, using a halogenating reagent, such as N-bromosuccinimide, in the presence of a peroxide (e.g. benzoyl peroxide) and in a suitable solvent such as a halogenated hydrocarbon

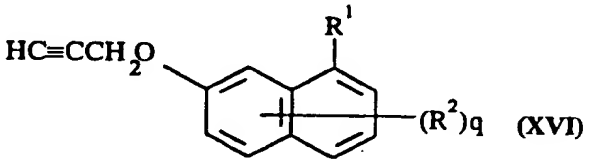
(e.g. carbon tetrachloride) with the mixture heated at reflux with simultaneous irradiation.

Step (vii) comprises treating a compound of formula (xv) with a cyanide (e.g. potassium cyanide) in an alcohol (e.g. methanol) and heating the mixture at reflux until the reaction is complete.

Compounds of formula (IX) are either known in the art (J.Org.Chem., (1957), 22, 193), or may be prepared by methods analogous to those described in the art for preparing the known compounds of formula (IX).

According to another general process (B), a compound of formula (I) may be converted to another compound of formula (I). Thus, for example, a fully unsaturated compound of formula (I) (i.e. where both dotted lines in the naphthalene portion of the tricycle indicate the presence of additional bonds and the dotted line in the oxygen-containing ring of the tricycle indicates the presence of an additional bond) may be reduced using conventional techniques to a corresponding partially or fully saturated compound of formula (I). The reduction may conveniently be effected by catalytic hydrogenation, for example using 10% palladium on carbon. The hydrogenation may be effected in an alcohol solvent (e.g. ethanol), conveniently at about ambient temperature.

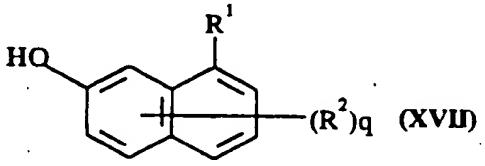
According to another process (C), a fully unsaturated compound of formula (I) in which n is 1 may be prepared by cyclising a compound of formula (XVI)



(XVI)

The reaction may conveniently be effected by heating a compound of formula (XVI) (e.g. under reflux) in a suitable solvent such as a halogenated hydrocarbon (e.g. bromobenzene).

A compound of formula (XVI) may be prepared by the alkylation of a compound of formula (XVII)

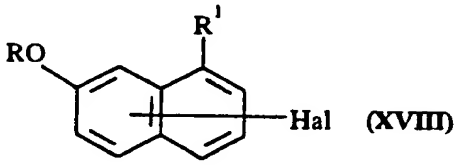


(XVII)

using an alkyl halide $HalCH_2C{\equiv}CH$ (where Hal is a halogen atom, e.g. bromine). The alkylation may be effected under conventional conditions, for example in a suitable solvent such as dimethylformamide and in the presence of a suitable base such as an alkali or alkaline earth metal carbonate or bicarbonate (e.g. potassium carbonate) at a temperature of from about 50°C to about 150°C.

A compound of formula (XVII) wherein R^2 represents hydrogen is described in Example 44 of EP-A-0562956.

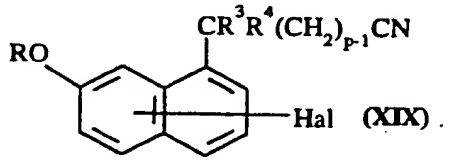
A compound of formula (XVII) wherein R^2 represents halogen can be prepared from a corresponding compound of formula (XVIII)



(XVIII)

wherein R represents a C_{1-4}alkyl group, typically methyl and Hal represents a halogen atom substantially as hereinbefore described. Aptly the preparation of a compound of formula (XVII) wherein R^2 represents Hal, from a compound of formula (XVIII), is achieved by removal of alkyl substituent R, aptly by treatment with a boron trihalide, e.g. boron tribromide, in a haloginated solvent, such as dichloromethane, at ambient temperature.

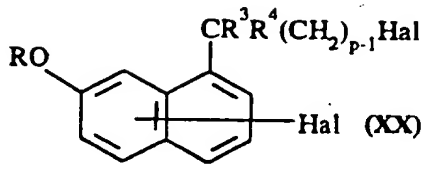
Suitably a compound of formula (XVIII) is prepared from a compound of formula (XIX)



(XIX).

employing sequential reflux steps; initially reflux in the presence of borane in an ether solvent, such as tetrahydrofuran, under an inert atmosphere, appropriately nitrogen; subsequently the reflux mixture is acidified, followed by reflux for a few minutes; finally, the mixture is basified and subjected to further reflux. A corresponding amine is thus obtained which is subsequently acylated employing conventional techniques as hereinbefore described.

A compound of formula (XIX) is aptly prepared from a compound of formula (XX)

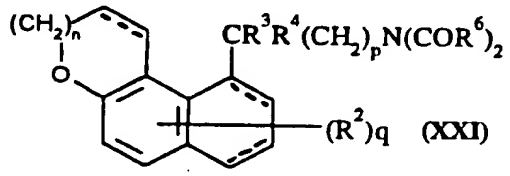


(XX)

suitably by reflux in the presence of an alcoholic solvent and an alkali metal cyanide.

A compound of formula (XX) may be prepared from a compound of formula (XI) as hereinbefore described, suitably employing conventional halogenating agents, such as NBS or the like.

According to another general process (D), a compound of formula (I) may be prepared from a compound of formula (XXI)



(XXI)

suitably by stirring at an elevated temperature, of the order of 60 to 100°C, for several hours. Conveniently, the reaction is carried out in the presence of an alcoholic solvent, e.g. methanol, and a basic medium, such as an alkali metal hydroxide, appropriately sodium hydroxide.

A compound of formula (XXI) can be prepared from a corresponding compound of formula (III), wherein A represents -CN. Suitably the preparation involves sequential reflux stages as substantially hereinbefore described with reference to a compound of formula (XIX).

According to another general process (E), a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the preparation of a compound of formula (I) it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed.J.F.W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene (John Wiley and Sons 1991).

As will be appreciated, in any of the general processes (A), (B), (C) or (D) described above it may be desirable or even necessary to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes (A), (B), (C) or (D).

Thus, according to a further aspect of the invention, the following reactions may, if desirable and/or if necessary, be carried out in any appropriate sequence subsequent to any of the processes (A), (B), (C) or (D):

(i) removal of any protecting groups; and

(ii) conversion of a compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt thereof.

Compounds of the invention may be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using chiral HPLC.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

Compounds of formulae (II) to (VII), (XIV), (XV) and (XXI) are novel intermediates and form further individual aspects of the present invention. Compounds of formula (VII) are particularly important intermediates for preparing compounds of formula (I). Compounds of formula (IX) are either known compounds described in J. Org. Chem. (1957), 22, 193 or may be

prepared by methods analogous to those described in the art for preparing the known compounds of formula (IX).

The invention is further illustrated by the following Examples which should not be construed as constituting a limitation thereto. Ammonia (NH_3) means aqueous ammonia (i.e. 0.880 NH_3). EtOAc means ethyl acetate. Chromatography was performed on silica (Merck 9385 unless otherwise stated). T.l.c. means thin layer chromatography.

Intermediate 1

1,2,7,8-Tetrahydro-6H-naphtho[2,1-b]furan-9-one

Pyridine (4 drops) was added to a stirring mixture of 4-(2,3-dihydro-benzofuran-5-yl)-butyric acid[1] (10.0g) and thionyl chloride (4.30ml) in diethyl ether (100ml). The mixture was heated under reflux with stirring for 1 hour, cooled to room temperature, and concentrated in vacuo. The residual yellow gum was diluted with dichloromethane (150ml) and tin (IV) chloride (5.70ml) was added dropwise maintaining the temperature at 5-10°C. The resulting mixture was stirred at room temperature for 3 hours, poured into ice-2N hydrochloric acid (150ml), and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2x100ml), and the combined organic solutions were washed with brine (100ml), dried ($MgSO_4$), and evaporated in vacuo to leave a black oil. The oil was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (15:85→20:80) to give the title compound as a white solid (607mg), m.p. 73-4°C.

Reference

1. Gagniant P., Gagniant D., Bull. Soc. Chim. Fr., (1955), 931.

Intermediate 2

(1,2,6,7-Tetrahydro-naphtho[2,1-b]furan-9-yl)-acetic acid methyl ester

A mixture of Intermediate 1 (1.75g), zinc (4.25g), iodine (50mg), methyl bromoacetate (1.10ml), diethyl ether (25ml) and toluene (25ml) was heated under reflux with stirring for 2 hours. The mixture was cooled to room temperature, treated with methanol (15ml) and filtered through Hyflo. The filtrate was evaporated in vacuo, and the residual oil was diluted with toluene (60ml). 4-Toluenesulphonic acid (100mg) was added and the mixture was heated at reflux with stirring for 1 hour. The mixture was cooled to room

temperature, evaporated to dryness, diluted with ethyl acetate (120ml) and washed successively with 10% hydrochloric acid (50ml), 2N aqueous sodium carbonate solution (50ml) and brine (25ml). The organic solution was dried ($MgSO_4$) and concentrated in vacuo to leave an amber gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (20:80) to give the title compound as a pale yellow oil (1.70g).
T.l.c. EtOAc : cyclohexane (20 : 80) Rf = 0.30.

Intermediate 3

Naphtho[2,1-b]furan-9-yl-acetic acid methyl ester

A mixture of Intermediate 2 (1.65g) and p-chloranil (4.15g) in xylenes (30ml) was heated under reflux with stirring for 18 hours. The mixture was cooled to room temperature and evaporated in vacuo to leave a black solid. The solid was treated with ethyl acetate (150ml) and 2N aqueous sodium carbonate (100ml) and the mixture was filtered. The organic phase was separated, washed with brine (50ml), dried ($MgSO_4$) and preabsorbed onto silica gel. Purification by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (15:85) gave the title compound as a red oil (1.44g).
T.l.c. EtOAc : cyclohexane (20 : 80) Rf = 0.40.

Intermediate 4

2-Naphtho[2,1-b]furan-9-yl-ethanol

A solution of lithium aluminium hydride in tetrahydrofuran (1.0M x 6.60ml) was added steadily to a cold (10°C), stirring solution of Intermediate 3 (1.44g) in tetrahydrofuran (30ml). The pale yellow solution was stirred at room temperature for 0.5 hours, and then cooled to 4°C and treated with ethyl acetate (10ml). After a further 10 minutes, 2N hydrochloric acid (30ml) was added, and the mixture was extracted with ethyl acetate (2x30ml). The combined organic extracts were washed with brine (1x20ml), dried ($MgSO_4$), and evaporated in vacuo to leave a yellow gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (40:60) to give the title compound as white needles (1.07g), m.p. 79-81°C.

Intermediate 5

2-(2-Naphtho[2,1-b]furan-9-yl-ethyl)-isoindole-1,3-dione

A solution of Intermediate 4 (300mg) in tetrahydrofuran (2.5ml) was added to a cold (4°C), stirring solution of phthalimide (270mg), triphenyl phosphine (482mg) and diethylazodicarboxylate (290µl) in tetrahydrofuran (6ml). The yellow solution was stirred at room temperature for 6 hours, preabsorbed onto silica gel and purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (25:75) to give the title compound as a white powder (383mg), m.p. 154-5°C.

Intermediate 6

(1,2-Dihydro-naphtho[2,1-b]furan-9-yl)-acetic acid methyl ester

A mixture of Intermediate 2 (1.55g), p-chloranil (1.87g) and xylenes (30ml) was heated at reflux with stirring for 1 hour. The solvent was evaporated in vacuo, and the black residue was diluted with ethyl acetate (100ml) and 2N aqueous sodium hydroxide solution (50ml). The mixture was filtered, and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2x30ml) and the combined organic solutions were washed with brine (1x50ml), dried ($MgSO_4$) and evaporated in vacuo to leave a dark gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (15:85) to give the title compound as a gum which solidified on standing (980mg).

T.l.c. EtOAc : cyclohexane (20 : 80) Rf = 0.35.

Intermediate 7

2-(1,2-Dihydro-naphtho[2,1-b]furan-9-yl)-acetamide

A mixture of Intermediate 6 (970mg), lithium hydroxide monohydrate (500mg), tetrahydrofuran (10ml) and water (5ml) was stirred at room temperature for 4 hours. The mixture was acidified with 10% hydrochloric acid (25ml) and extracted with ethyl acetate (4x25ml). The combined organic extracts were washed with brine (15ml), dried ($MgSO_4$), and evaporated in vacuo to leave a solid (600mg). The solid was dissolved in tetrahydrofuran (20ml) and treated with carbonyldiimidazole (1.28g). This mixture was stirred at room temperature for 1 hour and then treated with ammonia (5ml). The mixture was allowed to stand at room temperature for 16 hours and then diluted with water (60ml) and extracted with ethyl acetate containing 5% methanol (3x60ml). The combined organic extracts were washed with brine (20ml), dried ($MgSO_4$)

and evaporated in vacuo to leave a brown powder. This was pre-absorbed onto silica gel and purified by column chromatography eluting with a mixture of ethyl acetate and methanol (95:5) to give the title compound as a white powder (290mg), m.p. 224-6°C.

Intermediate 8

7-Fluoro-6-methoxy-4-methyl-1,2-dihydro-naphthalene

A suspension of anhydrous cerium (III) chloride (16.9g) in tetrahydrofuran (160ml) was stirred at room temperature under nitrogen for 2 hours. The suspension was cooled to -78°C and treated with methyllithium (30.0ml x 1.4M) in diethyl ether. After 0.5h at -78°C, a solution of 6-fluoro-7-methoxy-3,4-dihydro-2H-naphthalen-1-one [2] (6.45g) in tetrahydrofuran (25ml) was added and the mixture was stirred at -78°C for 4 hours. The mixture was stirred at room temperature for 2 hours, and then treated with 10% hydrochloric acid (100ml). The mixture was extracted with ethyl acetate (1x50ml, 2x30ml), and the combined organic extracts were washed with brine (1x50ml). The solvent was evaporated in vacuo to leave a red oil which was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (20:80) to give the title compound as a pale yellow gum (1.42g).

T.l.c. EtOAc : cyclohexane (1 : 1) Rf=0.70.

Reference

2. Buu-Hoi et al., J. Org. Chem., (1957), 22, 193.

Intermediate 9

6-Fluoro-7-methoxy-1-methyl-naphthalene

A solution of Intermediate 8 (1.40g) and p-chloranil (2.23g) in xylenes (17ml) was heated at reflux with stirring under nitrogen for 16 hours. The solvent was evaporated in vacuo and the residue was suspended in dichloromethane (30ml) and filtered. The filtrate was evaporated in vacuo to leave a red oil which was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (5:95) to give the title compound as a solid (970mg), m.p. 76-78°C.

Intermediate 10

3-Fluoro-8-methyl-naphthalen-2-ol

A solution of boron tribromide in dichloromethane (1.0M x 6.56ml) was added to a cold, stirring solution of Intermediate 9 (960mg) in dichloromethane (20ml) maintained at 0°C. The mixture was stirred at room temperature for 2 hours, cooled to 4°C and treated cautiously with methanol (2ml). The solvent was evaporated in vacuo and the residue was treated with 2M hydrochloric acid (30ml) and extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with brine (1x20ml), dried ($MgSO_4$), and evaporated in vacuo to leave the title compound as an oil (880mg).
T.l.c. EtOAc : cyclohexane (1 : 9) Rf=0.30.

Intermediate 11
7-(2,2-Diethoxy-ethoxy)-6-fluoro-1-methyl-naphthalene

A mixture of Intermediate 10 (881mg), anhydrous potassium carbonate (828mg) and bromoacetaldehyde diethyl acetal (902µl) in dimethylformamide (6ml) was heated at 130°C with stirring for 17 hours. Upon cooling to room temperature, the mixture was poured into water (60ml) and extracted with diethyl ether (3x30ml). The combined organic extracts were washed with 2M aqueous sodium hydroxide (1x30ml) and brine (1x30ml), dried ($MgSO_4$) and concentrated in vacuo to leave a dark oil. The oil was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (7:93) to give the title compound as a pale yellow oil (1.19g).
T.l.c. EtOAc : cyclohexane (1 : 9) Rf=0.45.

Intermediate 12
4-Fluoro-9-methyl-naphtho[2,1-b]furan

A solution of the Intermediate 11 (1.15g) in toluene (2ml) was added in one portion to a rapidly stirring mixture of polyphosphoric acid (2g) and toluene (10ml) maintained at reflux under nitrogen. After 2 hours, the mixture was poured into water (60ml) containing 2M aqueous sodium hydroxide (10ml) and extracted with diethyl ether (3x30ml). The combined organic extracts were washed with brine (1x25ml), dried ($MgSO_4$) and concentrated in vacuo to leave a yellow gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (5:95) to give the title compound as a yellow solid (704mg), m.p. 83-85°C.

Intermediate 13

(4-Fluoro-naphtho[2,1-b]furan-9-yl)-acetonitrile

A mixture of Intermediate 12 (700mg), N-bromosuccinimide (685mg) and benzoyl peroxide (50mg) in carbon tetrachloride (15ml) was heated at reflux with stirring under nitrogen and simultaneously irradiated with a 50W halogen lamp. After 4 hours, the mixture was cooled to room temperature, filtered, and the filtrate was evaporated in vacuo to leave a solid. The solid was dissolved in ethyl acetate (60ml) and washed successively with water (2x15ml) and brine (25ml), dried ($MgSO_4$) and evaporated in vacuo to leave a solid (1.19g). The solid was suspended in wet methanol (20ml) and treated with potassium cyanide (260mg). This mixture was heated at reflux with stirring under nitrogen for 2 hours and then evaporated to dryness in vacuo, treated with water (40ml) and extracted with ethyl acetate (3x25ml). The combined organic extracts were washed with brine (1x25ml), dried ($MgSO_4$) and evaporated in vacuo to leave a solid. The solid was preabsorbed onto silica gel and purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (25:75) to give the title compound as a pale yellow solid (396mg), m.p. 179-180°C.

Intermediate 14

2,3,8,9-Tetrahydro-1H,7H-benzo[f]chromen-10-one

Pyridine (4 drops) was added to a stirring mixture of 4-chroman-6-yl-butyric acid[3] (10.4g) and thionyl chloride (4.02ml) in diethyl ether (100ml). The mixture was heated under reflux with stirring for 1 hour and evaporated in vacuo. The residue was taken up in dichloromethane (150ml), cooled to 0-5°C, and treated with stannic chloride (5.50ml). The resulting mixture was stirred at room temperature for 2 hours, poured into ice-2N hydrochloric acid (150ml), and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2x100ml), and the combined organic solutions were washed with brine (100ml), dried ($MgSO_4$), and evaporated in vacuo to leave a black gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (15:85→20:80) to give the title compound as a pale yellow gum (584mg).

T.l.c. EtOAc : cyclohexane (3 : 7) Rf=0.60.

Reference

3. Chatelus, Ann. Chim. (Paris), (1949), 12, 505.

Intermediate 15

(2,3,7,8-Tetrahydro-1H-benzo[f]chromen-10-yl)-acetic acid methyl ester

A mixture of Intermediate 14 (580mg), zinc dust (1.25g), iodine (ca. 50mg), methylbromoacetate (323µl), diethyl ether (6ml) and toluene (6ml) was heated under reflux with stirring for 4 hours. Upon cooling to room temperature, methanol (10ml) was added and the mixture was filtered through hyflo. The solvent was evaporated in vacuo and the residue was treated with toluene (25ml) and 4-toluenesulphonic acid (50mg) and heated under reflux with stirring for 1 hour. Upon cooling to room temperature, the solvent was evaporated in vacuo and the residue was diluted with 10% hydrochloric acid (30ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were washed with brine (20ml), dried ($MgSO_4$), and then evaporated in vacuo to leave a yellow gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (10:90) to give the title compound as a pale yellow gum (350mg).

T.l.c. EtOAc : cyclohexane (1 : 9) Rf=0.35.

Intermediate 16

(2,3-Dihydro-1H-benzo[f]chromen-10-yl)-acetic acid methyl ester

A mixture of Intermediate 15 (350mg) and p-chloranil (365mg) in xylenes (10ml) was heated at reflux with stirring under a nitrogen atmosphere for 4 hours. Additional p-chloranil (360mg) was added, and the mixture was heated at reflux with stirring for a further 16 hours. The solvent was evaporated in vacuo, and the residue was preabsorbed onto silica gel and purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (10:90) to give the title compound as a yellow gum (209mg).

T.l.c. EtOAc : cyclohexane (2 : 8) Rf=0.30.

Intermediate 17

2-(2,3-Dihydro-1H-benzo[f]chromen-10-yl)-ethanol

A solution of lithium aluminium hydride in tetrahydrofuran (1.0M x 1.50ml) was added dropwise to a stirring solution of Intermediate 16 (200mg) in tetrahydrofuran (6ml) maintained at 4°C. The mixture was stirred at room temperature for 4 hours, then cooled to 4°C (ice-water) and treated with ethyl

acetate (1ml) followed by 2N hydrochloric acid (25ml). The mixture was extracted with ethyl acetate (3x15ml), and the combined organic extracts were washed with brine (1x15ml), dried ($MgSO_4$), and evaporated in vacuo to leave a yellow gum. The gum was purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (30:70) to give the title compound as a colourless gum (100mg).

T.l.c. EtOAc : cyclohexane (3 : 7) Rf=0.40.

Intermediate 18

2-(2,3-Dihydro-1H-benzo[f]chromen-10-yl)-ethylamine

A solution of Intermediate 17 (100mg) in tetrahydrofuran (2ml) was added to a cold, stirring solution of triphenylphosphine (149mg), phthalimide (84mg) and diethylazodicarboxylate (90µl) maintained at 4°C. The mixture was stirred at room temperature for 4 hours and then evaporated onto silica gel and purified by column chromatography eluting with a mixture of ethyl acetate and cyclohexane (20:80) to give a white solid (150mg). A solution of the solid in a mixture of hydrazine hydrate (1ml), water (4 drops) and ethanol (5ml) was heated at reflux with stirring for 4 hours. The solvent was evaporated in vacuo, and the residue was washed with ethyl acetate (3x15ml). The combined organic washings were evaporated in vacuo to leave a yellow gum which was purified by column chromatography eluting with a mixture of 5% ammoniacal methanol and dichloromethane (20:80) to give the title compound as a white semi-solid (79mg).

T.l.c. 5% ammoniacal methanol : dichloromethane (1 : 4) Rf=0.30.

Intermediate 19

N-[2-[7-(Prop-2-ynyloxy)-naphthalen-1-yl]-ethyl]-acetamide

A mixture of N-[2-(7-hydroxy-naphthalen-l-yl)-ethyl]-acetamide (Example 44 in EP-A-0562956) (350mg), anhydrous potassium carbonate (414mg), propargyl bromide (80wt% in toluene; 170µl) and dimethylformamide (6ml) was stirred at 110°C for 3 hours and then allowed to stand at room temperature for 15 hours. The mixture was diluted with water (30ml) and extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with brine (20ml), dried ($MgSO_4$) and evaporated in vacuo to leave a yellow oil. The oil was purified by

column chromatography eluting with a mixture of methanol and ethyl acetate (3:97) to give the title compound as a pale yellow gum (380mg).
T.l.c. methanol : EtOAc (1 : 19) Rf 0.55.

Intermediate 20
7-Fluoro-6-methoxy-4-methyl-1,2-dihydro-naphthalene

To a cold (-78°C) stirred solution of cerium(III)chloride (dry, 122.8g) in dry tetrahydrofuran (900ml), methyllithium (1.4M in diethyl ether, 200ml) was added dropwise. After 1 hour, a solution of 6-fluoro-7-methoxy-3,4-dihydro-2H-naphthalen-1-one[2] (44.1g) in dry tetrahydrofuran (300ml) was added dropwise. The mixture was allowed to warm to 20°C and was stirred for 16 hours, then 2N hydrochloric acid (400ml) was added. After 1 hour the layers were separated and the organic layer washed with brine. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate/cyclohexane 1:3 to give the title compound as a pale yellow solid (41.2g).
T.l.c. SiO_2 (ethyl acetate/cyclohexane 1:3), Rf 0.33
N.m.r. ($CDCl_3$) δ 2.04 (3H,m), 2.22 (2H,m), 2.66 (2H,t), 3.90 (3H,s), 5.82 (1H,br d), 6.85-6.9 (2H,2xd).

Intermediate 21
3-Fluoro-8-methyl-naphthalen-2-ol

A solution of Intermediate 20 (41.2g) and p-chloranil (65.9g) in xylenes (500ml) was heated at reflux with stirring for 5 hours. Upon cooling to room temperature, the solvent was evaporated in vacuo, the residue suspended in dichloromethane (300ml) and then filtered. The precipitate was washed with dichloromethane (3x100ml), and the combined organic extracts were evaporated in vacuo. The residue was purified by column chromatography on silica eluting with ethyl acetate/cyclohexane 1:20 to give the naphthalene as a brown solid (38.3g).

The naphthalene (38.3g) was dissolved in dichloromethane (500ml), and the stirred solution cooled to 0°C. Boron tribromide (1M in dichloromethane, 250ml) was added, the cooling bath was removed and stirring maintained at room temperature for 18 hours. The reaction mixture was cooled (0°C) and

methanol (100ml) was added dropwise. The solvent was evaporated in vacuo and the residue treated with 2N hydrochloric acid and then extracted with ethyl acetate. The dried extracts were evaporated and the residue chromatographed on silica gel. Elution with ethyl acetate/cyclohexane 1:20 gave the title compound as a pale brown solid (34.8g).

T.l.c. SiO_2 (ethyl acetate/cyclohexane 1:20), Rf 0.20

N.m.r. ($CDCl_3$) δ 2.61 (3H,s), 5.43 (1H,d), 7.22-7.3 (2H,m), 7.46-7.6 (3H,m).

Intermediate 22

7-(2,2-Diethoxy-ethoxy)-6-fluoro-1-methyl-naphthalene

A mixture of Intermediate 21 (20g), potassium carbonate (18.8g) and bromoacetaldehyde diethylacetal (20.5ml) in dry dimethylformamide (100ml) was heated to 110°C, with stirring, for 21 hours. The mixture was cooled and poured into water and then extracted with ethyl acetate. The organic phase was washed with sodium hydroxide, and then with brine. The dried extracts were evaporated and the residue chromatographed on silica gel. Eluting with ethyl acetate/cyclohexane 1:10 gave the title compound as a pale yellow oil (33.4g).

T.l.c. SiO_2 (ethyl acetate/cyclohexane 1:10), Rf 0.53

N.m.r. ($CDCl_3$) δ 1.28 (6H,t), 3.64-3.90 (4H,m), 4.20 (2H,d), 4.95 (1H,t), 7.25-7.32 (2H,m), 7.35 (1H,br d), 7.46 (1H,d), 7.53-7.6 (1H,m).

Intermediate 23

4-Fluoro-9-methyl-naphtho[2,1-b]furan

A solution of Intermediate 22 (33.4g) in toluene (100ml) was added to a rapidly stirring mixture of polyphosphoric acid (60g) and toluene (300ml) at 60°C. On completion of addition, the mixture was heated at reflux for 5 hours, then cooled to room temperature. The reaction mixture was poured into water (750ml) containing 2M sodium hydroxide (300ml) and extracted with diethyl ether (2x300ml). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was recrystallised from a mixture of dichloromethane and cyclohexane to give the title compound as an orange solid (12.35g).

T.l.c. SiO_2 (ethyl acetate/cyclohexane 1:10), Rf 0.5

N.m.r. ($CDCl_3$) δ 2.91 (3H,s), 7.32-7.47 (3H,m), 7.49 (1H,dd), 7.74 (1H,dd), 7.83 (1H,d).

Intermediate 24

9-Bromomethyl-4-fluoro-naphtho[2,1-b]furan

A stirred mixture of Intermediate 23 (10.0g), N-bromosuccinimide (9.79g) and benzoyl peroxide (100mg) in carbon tetrachloride (200ml) was simultaneously heated at reflux and irradiated with a 50W tungsten lamp for 2 hours. Heating at reflux was continued for a further 15 hours, then the reaction mixture was cooled to room temperature, filtered and evaporated in vacuo. The residue was dissolved in ethyl acetate (500ml), washed with water (2x150ml) and brine (100ml), dried ($MgSO_4$) and evaporated in vacuo. The crude material was purified by column chromatography on silica eluting with cyclohexane, followed by recrystallisation from cyclohexane/dichloromethane, to yield the title compound as a white powder (6.21g).

T.l.c. SiO_2 (cyclohexane), Rf 0.27

N.m.r. ($CDCl_3$) δ 5.10 (2H,s), 7.43-7.50 (2H,m), 7.58-7.63 (2H,m), 7.89 (1H,dd), 7.9 (1H,d).

Intermediate 25

(4-Fluoro-naphtho[2,1-b]furan-9-yl)-acetonitrile

Intermediate 24 (1.2g) was dissolved in methanol (25ml) and treated with potassium cyanide (308mg). The mixture was heated at reflux with stirring under nitrogen for 3 hours and then evaporated to dryness in vacuo. The residue was treated with water (50ml) and extracted with ethyl acetate (2x100ml). The combined extracts were dried and concentrated to dryness under vacuo. The solid was purified by column chromatography on silica, eluting with cyclohexane:ethyl acetate (20:1), to give the title compound as a white powder (770mg).

T.l.c. (SiO_2) cyclohexane:ethyl acetate (20:1), Rf 0.12

N.m.r. ($CDCl_3$) δ 4.36 (2H,s), 7.35 (1H,t), 7.47-7.58 (2H,m), 7.69 (1H,br d), 7.88-7.94 (2H,d+br d).

Intermediate 26

Cyclopropanecarboxylic acid cyclopropanecarbonyl-2-(4-fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]amide

A solution of borane in tetrahydrofuran (1M, 8.55ml) was added to a stirred solution of Intermediate 25 (770mg) in tetrahydrofuran (25ml). The mixture was heated at reflux under a nitrogen atmosphere for 3 hours. The reaction mixture was cooled to room temperature, treated cautiously with 2N hydrochloric acid (10ml) and then heated to reflux for 5 minutes. The mixture was cooled, basified with 2N sodium hydroxide (35ml) and heated to reflux for a further 30 minutes. The reaction mixture was then cooled to room temperature and partitioned between water (70ml) and ethyl acetate (100ml). The aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried and concentrated to dryness in vacuo. The crude product was purified using column chromatography on silica using dichloromethane: ethanol:ammonia (100:8:1) as eluent to give the amine as a yellow oil (730mg).
T.l.c. (SiO_2) dichloromethane:ethanol:ammonia (100:8:1), Rf 0.20

A solution of the amine (60mg) and diisopropylethylamine (68µl) in dichloromethane was treated with cyclopropancarbonylchloride (26µl). The reaction mixture was stirred at room temperature for 3 hours. The mixture was poured into water (20ml) and extracted with ethyl acetate. The combined extracts were washed with brine, dried and concentrated to give an oil. The oil was purified using column chromatography on silica with an eluent of cyclohexane and ethyl acetate, to give the title compound as a white solid (49mg).
T.l.c. (SiO_2) Ethyl acetate, Rf 0.64
N.m.r. ($CDCl_3$) δ 0.92 (4H,m), 1.17 (4H,m), 2.18 (2H,m), 3.55 (2H,½AABB'), 4.20 (2H,½AA'BB'), 7.35-7.50 (3H,m), 7.78 (1H,dd), 7.88-7.95 (2H,m).

Intermediate 27
6-Fluoro-7-methoxy-1-methyl-naphthalene
p-Chloranil (10.7g) was added at room temperature to a stirring solution of Intermediate 8 (6.70g) in xylenes (70ml). The dark mixture was heated at reflux with stirring under a nitrogen atmosphere for 14 hours. The solvent was evaporated in vacuo to leave a dark red solid which was suspended in dichloromethane (80ml) and filtered. The filter pad was washed with additional dichloromethane (2x20ml) and the combined organic filtrates were evaporated in vacuo to leave a red oil. The oil was purified by column chromatography

(SiO_2) eluting with a mixture of ethyl acetate and cyclohexane (4:96) to give the title compound as a red solid (4.80g).

T.l.c. SiO_2: 5% Ethyl acetate-95% cyclohexane, Rf 0.30

N.m.r. ($CDCl_3$) δ 2.67 (3H,s), 4.02 (3H,s), 7.23-7.33 (3H,m), 7.46 (1H,d), 7.58 (1H,m).

Intermediate 28

1-Bromomethyl-6-fluoro-7-methoxy-naphthalene

A mixture of Intermediate 27 (890mg), benzoyl peroxide (50mg) and N-bromosuccinimide (917mg) in carbon tetrachloride (20ml) was irradiated with a 50W halogen lamp and heated at reflux with stirring under a nitrogen atmosphere for 4 hours. Upon cooling to room temperature, the mixture was filtered and evaporated in vacuo to leave a solid which was dissolved in ethyl acetate (40ml) and washed successively with water (1x20ml) and brine (1x20ml). The organic solution was dried ($MgSO_4$) and evaporated in vacuo to leave the title compound as a yellow solid (1.29g).

T.l.c. SiO_2: 15% Ethyl acetate-85% cyclohexane, Rf 0.30

N.m.r. ($CDCl_3$) δ 4.07 (3H,s), 4.92 (2H,s), 7.32 (1H,t), 7.34-7.46 (3H,m), 7.72 (1H,br d).

Intermediate 29

(6-Fluoro-7-methoxy-naphthalen-1-yl)acetonitrile

A mixture of Intermediate 28 (1.25g) and potassium cyanide (457mg) in methanol (25ml) containing water (0.5ml) was heated to reflux with stirring. After 1 hour, the solvent was evaporated in vacuo and the residue was diluted with water (30ml) and extracted with ethyl acetate (3x30ml). The combined organic extracts were washed with brine (1x30ml), dried ($MgSO_4$) and evaporated in vacuo to leave a yellow solid which was purified by column chromatography (SiO_2) eluting with a mixture of ethyl acetate and cyclohexane (25:75) to give the title compound as an off-white solid (419mg), m.p. 148-50°C.

T.l.c. SiO_2: 25% Ethyl acetate-75% cyclohexane, Rf 0.30

Intermediate 30

N-[2-(6-Fluoro-7-methoxy-naphthalen-1-yl)-ethyl]-acetamide

A solution of borane in tetrahydrofuran (1.0M x 4.80ml) was added to a stirring solution of Intermediate 29 (400mg) in tetrahydrofuran (25ml). The mixture was heated to and maintained at reflux with stirring for 2 hours. Upon cooling to room temperature, the mixture was cautiously treated with 10% hydrochloric acid (5ml) and refluxed for a further 10 minutes. The mixture was basified with 2M aqueous sodium hydroxide solution (15ml) and heated at reflux for a further 0.5 hours. The mixture was diluted with water (30ml) and extracted with ethyl acetate (3x30ml). The combined organic extracts were washed with brine (1x30ml), dried (Na_2SO_4) and evaporated in vacuo to leave a yellow oil. The oil was dissolved in dichloromethane (15ml), cooled to 10°C (water bath), and treated successively with diisopropylethylamine (648µl) and acetyl chloride (165µl). After 0.5 hours, the mixture was poured into dichloromethane (40ml) and washed successively with water (1x15ml) and brine (1x15ml), dried ($MgSO_4$) and evaporated in vacuo to leave a yellow solid. This was purified by column chromatography (SiO_2) eluting with ethyl acetate to give the title compound as a yellow solid (480mg).

T.l.c. SiO_2: 100% Ethyl acetate, Rf 0.30

N.m.r. ($CDCl_3$) δ 1.98 (3H,s), 3.25 (2H,m), 3.58 (2H,m), 4.10 (3H,s), 5.63 (1H,br s), 7.23-7.35 (2H,m), 7.48 (1H,d), 7.58-7.68 (2H,m).

Intermediate 31

N-[2-(6-Fluoro-7-hydroxy-naphthalen-1-yl)-ethyl]-acetamide

A solution of boron tribromide in dichloromethane (4.0ml x 1.0M) was added to a cold (4°C) stirring solution of Intermediate 30 (480mg) in dichloromethane (10ml). The mixture was stirred at room temperature for 2 hours, and then cautiously treated with methanol (1ml). The solvents were evaporated in vacuo to leave a dark gum which was treated with water (30ml) and extracted with ethyl acetate (3x15ml). The combined organic extracts were washed with brine (1x20ml), dried ($MgSO_4$) and evaporated in vacuo to leave a beige solid. This was pre-absorbed onto silica gel and purified by column chromatography (SiO_2) eluting with a mixture of methanol and ethyl acetate (2:98) to give the title compound as a white powder (310mg), m.p. 183-185°C.

T.l.c. SiO_2: 100% EtOAc, Rf 0.32

Intermediate 32

N-[2-[6-Fluoro-7-(prop-2-ynyloxy)-naphthalen-1-yl]-ethyl)-acetamide

A mixture of Intermediate 31 (300mg), anhydrous potassium carbonate (334mg) and 80wt% propargyl bromide in toluene (135µl) in anhydrous dimethylformamide (8ml) was heated at 110°C with stirring for 4 hours. The mixture was stirred at room temperature for 16 hours and then diluted with water (30ml) and extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with brine (1x20ml), dried ($MgSO_4$) and evaporated in vacuo to leave a brown solid. The solid was purified by column chromatography (SiO_2) eluting with ethyl acetate to give the title compound as a white solid (347mg), m.p. 139-140°C.

T.l.c. SiO_2: 100% Ethyl acetate, Rf 0.30

Example 1

N-(2-Naphtho[2,1-b]furan-9-yl-ethyl)-acetamide

A solution of Intermediate 5 (370mg), hydrazine hydrate (1.5ml) and ethanol (15ml) was heated at reflux with stirring for 3 hours. The solvent was evaporated in vacuo, and the residual white solid was suspended in ethyl acetate (20ml) and filtered. The solid was washed with further ethyl acetate (2x10ml), and the combined filtrates were concentrated in vacuo to leave a pale yellow gum. The gum was purified by column chromatography eluting with a mixture of 5% ammonical methanol and dichloromethane (10:90) to give a colourless gum (131mg). The gum was dissolved in a mixture of diisopropylethylamine (320µl) and dichloromethane (4ml), cooled to 4°C and treated with acetyl chloride (55µl). After 0.25 hours, water (10ml) was added, the organic phase was separated and the aqueous phase was extracted with dichloromethane (2x10ml). The combined organic solutions were dried ($MgSO_4$) and evaporated in vacuo to leave a white semi solid which was purified by column chromatography eluting with ethyl acetate to give the title compound as a white solid (140mg) m.p. = 150-1°C.

N.m.r. ($CDCl_3$) δ 1.97 (3H, s, 3.53 (2H, t), 3.71 (2H, q), 5.6 (1H, brs) and 7.4-7.9 (7H, m).

Example 2

N-[2-(1,2,6,7,8,9-Hexahydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide

A solution of Example 1 (80mg) in ethanol (5ml) was hydrogenated at 1 atmosphere and room temperature over 10% palladium on carbon (20mg) for 64 hours. The mixture was filtered through Hyflo, and the filter pad was washed with ethanol (3x10ml). The solvent was evaporated in vacuo and the residual colourless gum was purified by column chromatography eluting with ethyl acetate to give the title compound as a colourless gum (68mg).

T.l.c. EtOAc Rf = 0.20.

N.m.r. ($CDCl_3$) δ 1.7-1.9 (6H, m), 1.97 (3H, s), 2.6-2.8 (3H, m, 3.0-3.3 (2H), 3.35 (2H, m), 4.4-4.65 (2H, m), 5.5 (1H, brs), 6.59 (1H, d) and 6.83 (1H, d).

Example 3

N-[2-(1,2-Dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide

A solution of borane in tetrahydrofuran (1.0M x 5.0ml) was added to a stirring suspension of Intermediate 7 (280mg) in tetrahydrofuran (10ml). The solid dissolved and the solution was heated at reflux with stirring for 20 hours. Upon cooling to room temperature, 10% hydrochloric acid (10ml) was cautiously added, and the mixture was brought to reflux for 5 minutes, recooled to room temperature, and treated with 2N aqueous sodium hydroxide solution (20ml). The mixture was extracted with ethyl acetate (3x20ml), and the combined organic extracts were washed with brine (1x10ml), dried ($MgSO_4$), and evaporated in vacuo to leave a beige solid (270mg). The solid was dissolved in dichloromethane (8ml) and treated successively at room temperature with diisopropylethylamine (665µl) and acetyl chloride (113µl). After 15 minutes, water (10ml) was added and the mixture was extracted with dichloromethane (2x15ml). The combined organic extracts were washed with brine (1x10ml), dried ($MgSO_4$), and evaporated in vacuo to leave a beige solid which was purified by column chromatography eluting with a mixture of methanol and ethyl acetate (5:95) to give the title compound as white platelets from ethyl acetate/cyclohexane (250mg), m.p. 149-150°C.

N.m.r. ($CDCl_3$) δ 1.97 (3H,s), 3.22 (2H,t), 3.55 (2H,m), 3.83 (2H,t), 5.55 (1H,brs), 4.61 (2H,t) and 7.1-7.7 (5H,m).

Example 4

N-[2-(4-Fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide

A solution of borane in tetrahydrofuran (1.0M x 4.50ml) was added to a stirring solution of Intermediate 13 (390mg) in tetrahydrofuran (12ml) and the mixture was heated at reflux with stirring for 2 hours. The mixture was cooled to room temperature, treated cautiously with 2M hydrochloric acid (5ml) and then heated under reflux with stirring for 5 minutes. The mixture was basified with 2M aqueous sodium hydroxide (15ml) and heated at reflux for a further 0.5 hours. Upon cooling to room temperature, the mixture was poured into water (30ml) and extracted with ethyl acetate (3x25ml). The combined organic extracts were washed with brine (1x25ml), dried ($MgSO_4$) and then evaporated in vacuo to leave a yellow gum (273mg). The gum was dissolved in a mixture of dichloromethane (12ml) and diisopropylethylamine (512µl) and treated with acetyl chloride (105µl). After 0.5 hours, the mixture was poured into water (30ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were washed with brine (1x20ml), dried ($MgSO_4$) and evaporated in vacuo to leave a solid which was purified by column chromatography eluting with ethyl acetate to give the title compound as a white powder (210mg), m.p. 177-178°C.

N.m.r. ($CDCl_3$) δ 1.98 (3H), 3.50 (2H,t), 3.68 (2H,m), 5.6 (1H,brs) and 7.3-7.9 (6H,m).

Example 5

N-[2-(4-Fluoro-1,2-dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide

A solution of Example 4 (85mg) in ethanol (6ml) was hydrogenated at room temperature and atmospheric pressure over a stirring suspension of 10% palladium on carbon (40mg) for 4 hours. The mixture was filtered through Hyflo and the pad was washed with ethanol (2x3ml). The combined organic filtrates were evaporated in vacuo to leave a white powder which was purified by column chromatography eluting with a mixture of methanol and ethyl acetate (2:98) to give the title compound as a white powder (30mg), m.p. 174-176°C.

N.m.r. ($CDCl_3$) δ 1.97 (3H,s), 3.27 (2H,t), 3.53 (2H,q), 3.90 (2H,t), 4.82 (2H,t) and 7.2-7.7 (5H,m).

Example 6

N-[2-(2,3-Dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide

Acetyl chloride (30μl) was added to a cold, stirring solution of Intermediate 18 (79mg) and diisopropylethylamine (218μl) in dichloromethane (3ml) maintained at 4°C. The mixture was stirred at room temperature for 0.5 hours, and then diluted with water (15ml) and extracted with dichloromethane (3x15ml). The combined organic extracts were washed with brine (1x15ml), dried ($MgSO_4$), and evaporated in vacuo to leave a yellow semi-solid which was purified by column chromatography eluting with a mixture of methanol and ethyl acetate (5:95) to give the title compound as a white solid (83mg), m.p. 159-160°C.

N.m.r. ($CDCl_3$) δ 1.93 (3H,s), 2.07 (2H,m), 3.30 (2H,t), 3.4-3.6 (4H,m), 4.27 (2H,t) and 7.0-7.7 (5H,m).

Example 7

N-[2-(3H-Benzo[f]chromen-10-yl)-ethyl]-acetamide

A solution of Intermediate 19 (350mg) in bromobenzene (12ml) was degassed and then heated at reflux with stirring under nitrogen for 17 hours. The solvent was evaporated in vacuo to leave a brown gum. The gum was purified by column chromatography eluting with a mixture of methanol and ethyl acetate (3:97) to give the title compound as a white powder (182mg), m.p. 111-113°C.

Analysis Found: C,75.80; H,6.44; N,5.27;

$C_{17}H_{17}NO_2$ requires : C,76.38; H,6.41; N,5.24%.

Example 8

N-[2-(2,3-Dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide

A solution of Example 7 (150mg) in absolute ethanol (6ml) was hydrogenated at atmospheric pressure and room temperature over a stirring suspension of 10% palladium on carbon (30mg) for 0.5 hours. The catalyst was removed by filtration through Hyflo, and the filter pad was washed with ethanol (2x5ml). The combined organic filtrates were evaporated in vacuo to leave a white solid which was purified by column chromatography eluting with a mixture of methanol and ethyl acetate (5:95) to give the title compound as a white solid (144mg), m.p. 159-160°C.

N.m.r. ($CDCl_3$) δ 1.93 (3H, s), 2.07 (2H, m), 3.30 (2H, t), 3.4-3.6 (4H, m), 4.27 (2H, t) and 7.0-7.7 (5H, m).

Example 9

Cyclopropanecarboxylic acid[2-(4-fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]-amide

A solution of Intermediate 21 (49mg) in methanol (6ml) and 2N sodium hydroxide (4ml) was stirred at 80°C for 2 hours. The reaction mixture was then cooled to room temperature, concentrated to a smaller volume in vacuo, added to water and extracted with ethyl acetate. The combined extracts were dried and concentrated in vacuo to leave a solid, which was purified by column chromatography using silica and an eluent of cyclohexane:ethyl acetate (2:1) to give the title compound as a white solid (22mg), m.p. 196-197°C.

T.l.c. (SiO_2) cyclohexane:ethyl acetate 2:1, Rf 0.21

N.m.r. ($CDCl_3$) δ 0.76 (2H,m), 1.02 (2H,m), 1.30 (1H,m), 3.45-3.55 (2H,m), 3.65-3.75 (2H,m), 5.80 (1H,br s), 7.35-7.50 (3H,m), 7.75 (1H,t), 7.80 (1H,dd), 7.90 (1H,d).

Example 10

N-[2-(5-Fluoro-3H-benzo[f]chromen-10-yl)-ethyl-acetamide

A solution of Intermediate 27 (340mg) in bromobenzene (12ml) was degassed and heated at reflux with stirring for 5 hours. The solvent was evaporated in vacuo and the residual solid was purified by column chromatography (SiO_2) eluting with a mixture of methanol and ethyl acetate (2:98) to give the title compound as a white solid (247mg), m.p. 127-129°C.

T.l.c. SiO_2: 2% methanol-98% ethyl acetate, Rf 0.30

N.m.r. ($CDCl_3$) δ 1.95 (3H,s,), 3.35 (2H,t), 3.62 (2H,q), 4.79 (2H,dd), 5.52 (1H,br s), 5.95 (1H,dt), 7.2-7.33 (3H,m), 7.4 (1H,d), 7.59 (1H,m).

Example 11

N-[2-(5-Fluoro-2,3-dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide

A solution of Example 10 (175mg) in ethyl acetate (12ml) was hydrogenated over a stirring suspension of 10% palladium on carbon (30mg) at room temperature and atmospheric pressure for 3 hours. The catalyst was removed by filtration through a Hyflo pad and the pad was washed with ethyl acetate (3x20ml). The combined organic filtrates were evaporated in vacuo to leave a foam which was purified by column chromatography (SiO_2) eluting with a mixture of methanol and ethyl acetate (2:98) to give the title compound as a white solid (154mg; 88%), m.p. 111-113°C.

T.l.c. SiO_2: 2% methanol-98% ethyl acetate, Rf 0.25
N.m.r. ($CDCl_3$) δ 1.93 (3H,s), 2.11 (2H,m), 3.31-3.55 (6H,m), 4.37 (2H,t), 5.42 (1H,br s), 7.2-7.3 (2H,m), 7.33 (1H,d), 7.58 (1H,m).

Example 12

Compounds of formula (I) have been included in pharmacy formulations, and details of such formulations are given below.

TABLETS FOR ORAL ADMINISTRATION

A. Direct Compression

	% w/w
Active ingredient	32.7
Anhydrous lactose	36.8
Microcrystalline cellulose	25.0
Pregelatinised maize starch	5.0
Magnesium stearate	0.5

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets using a tablet machine fitted with suitable diameter punches.

A rotary machine may also be used for tabletting.

Tablets of various strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

B. Wet Granulation

Formulation (i)

	% w/w
Active ingredient	3.5
Lactose	73.25
Starch	15.0
Pregelatinised maize starch	7.5
Magnesium stearate	0.75

The active ingredient was sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets using suitable diameter punches.

A rotary machine may also be used for tabletting.

Tablets of various strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Formulation (ii)

	% w/w
Active ingredient/lactose granule*	93.0
Microcrystalline cellulose	5.5
Crosscarmellose sodium	1.0
Magnesium stearate	0.5

* Active ingredient/lactose granule	% w/w
Active ingredient	50.0
Lactose	50.0
Purified water	qs +

+ The water does not appear in the final product. Typical range 100-140g per kg of blend.

The active ingredient and lactose were mixed together and granulated by the addition of purified water. The granules obtained after mixing were dried and passed through a screen, and the resulting granules were then mixed with the other tablet core excipients. The mix is compressed into tablets.

A rotary machine may also be used for tabletting.

Tablets of various strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film-forming materials such as hydroxypropyl methylcellulose, preferably incorporating pigments in the formulation, using standard techniques. Alternatively the tablets may be sugar coated, or enteric coated.

Coating Suspension	% w/w
Hydroxypropyl methylcellulose	10.0
Opaspray	5.0
Purified water to	100.0++

or

Coating Suspension	% w/w
Opadry	10.0
Purified Water to	100.00 ++

++ The water does not appear in the final product.

COMPRESSION COATED TABLET

The active ingredient may also be formulated as a tablet core using conventional excipients such as fillers, binders, disintegrants and lubricants, and this core then compressed within an outer tablet (compression coated) using conventional excipients such as a pH-independent hydrophilic polymer, fillers, binders, disintegrants and lubricants. This outer coat may also contain active ingredient. The compression of both the core and the outer compression coat can be achieved using conventional tabletting machinery.

Such a dosage form can be designed so as to control the release of active ingredient as required.

EFFERVESCENT TABLET

	% w/w
Active ingredient	8.75
Sodium bicarbonate	41.03
Monosodium citrate anhydrous	41.22
Aspartame	2.5
Polyvinylpyrrolidone	2.0
Sodium benzoate	3.0
Orange flavour	1.0
Lemon flavour	0.5
Absolute alcohol for granulation	qs

The active ingredient, anhydrous monosodium citrate, sodium bicarbonate and aspartame were mixed together and granulated by the addition of a solution of the polyvinylpyrrolidone in the alcohol. The granules obtained after mixing were dried and passed through a screen, and the resulting granules were then mixed with the sodium benzoate and flavourings. The granulated material was compressed into tablets using suitable diameter punches.

A rotary machine may also be used for tabletting.

LIQUID AND CAPSULE FORMULATIONS FOR ORAL ADMINISTRATION

Liquid formulations were prepared by slow addition of active ingredient into the other ingredients at 35-50°C with constant mixing.

Example	A % w/w	B % w/w
Active ingredient	18.2	18.2
Oleic acid	60.985	68.485
Polyethylene glycol 600	7.3	7.3
Propylene glycol	6.0	6.0
Polysorbate 80	7.5	-
Ascorbyl palmitate	0.015	0.015

The liquid formulations were filled into hard gelatin capsules, the size of the capsule being used and the filler determining the possible dose of active ingredient per capsule.

CAPSULES

	% w/w
Active ingredient	24.5
Pregelatinised maize starch	75.0
Magnesium stearate	0.5

The active ingredient was sieved and blended with the excipients. The mix was filled into hard gelatin capsules using suitable machinery. The dose is determined by the fill weight and the capsule size.

SYRUP

	mg/5ml dose
Active ingredient	49.0
Hydroxypropyl methylcellulose (viscosity type 4000)	22.5
Buffer	qs
Flavour	qs
Colour	qs
Preservative	qs
Sweetener	qs
Purified water to	5.0ml

The hydroxypropyl methylcellulose was dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution was adjusted to volume and mixed. The syrup was clarified by filtration.

SUSPENSION

	mg/5ml dose
Active ingredient	49.0
Aluminium monostearate	75.0
Sweetening agent	qs
Flavour	qs
Colour	qs
Fractionated coconut oil to	5.0ml

The aluminium monostearate was dispersed in about 90% of the fractionated coconut oil. The resulting suspension was heated to 115°C while stirring and then cooled. The sweetening agent, flavour and colour were added and the active ingredient was suitably dispersed. The suspension was made up to volume with the remaining fractionated coconut oil and mixed.

SUB-LINGUAL TABLET

	% w/w
Active ingredient/lactose granule*	49.0
Compressible sugar	50.5
Magnesium stearate	0.5

The active ingredient was sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of various strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

A rotary machine may also be used for tabletting.

SUPPOSITORY FOR RECTAL ADMINISTRATION

Active ingredient	49.0mg
*Witepsol W32	1.0g

* A proprietary grade of Adeps Solidus Ph Eur

A suspension of the active ingredient in molten Witepsol was prepared and filled using suitable machinery, into 1g size suppository moulds.

INJECTION FOR SUBCUTANEOUS ADMINISTRATION

	mg/ml
Active ingredient	0.896
Sodium chloride intravenous infusion 0.9% w/v	to 1 ml

The active ingredient was dissolved in a portion of the sodium chloride intravenous infusion, the solution made to volume with the sodium chloride intravenous infusion, and the solution thoroughly mixed. The solution was filled

into clear, Type 1, glass 1ml ampoules and sealed by fusion of the glass under a nitrogen or air headspace. The ampoules were sterilised by autoclaving at 121°C for not less than 15 minutes. Alternatively the solution may be sterilised by filtration prior to filling aseptically into ampoules.

FOR INHALATION

Inhalation Cartridges

	mg/cartridge
Active ingredient (micronised)	0.56
Lactose	25.00

The active ingredient was micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend was filled into No 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges were administered using a powder inhaler such as the Glaxo Rotahaler.

Metered Dose Pressurised Aerosol

Suspension Aerosol	mg/metered dose	Per can
Active ingredient (micronised)	0.280	73.92mg
Oleic acid	0.020	5.28mg
Trichlorofluoromethane	23.64	5.67g
Dichlorodifluoromethane	61.25	14.70g

The active ingredient was micronised in a fluid energy mill to a fine particle size range. The oleic acid was mixed with the trichloromethane at a temperature of 10-15°C and the micronised drug was mixed into the solution with a high shear mixer. The suspension was metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension, were crimped onto the cans and the dichlorodifluoromethane was pressure filled into the cans through the valves.

NASAL SPRAY

	% w/v
Active ingredient	7.0
Sodium chloride	0.9
Purified water to	100
Shot weight	100mg (equivalent to 7mg active ingredient)

The active ingredient and sodium chloride were dissolved in a portion of the water, the solution made to volume with the water and the solution thoroughly mixed.

The pH may be adjusted to facilitate solution of the active ingredient, using acid or alkali and/or subsequently adjusted if necessary taking into account the pH for optimum stability. Alternatively, suitable buffer salts may be used. The solution may be preserved with, for example, benzalkanium chloride and phenylethyl alcohol, for a multi-dose nasal spray.

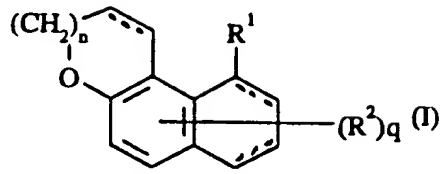
Example 13

Compounds of formula (I) have been shown to exhibit high affinity and selectivity for binding to melatonin receptors in chicken retinal membranes, measured according to the methods of Dubocovich and Takahashi (Proc. Natl. Acad. Sci. (1988), 84, 3916-3820). The compounds of formula (I) have either melatonin agonist or antagonist activity as demonstrated in rabbit retina, according to the methods of Dubocovich (J. Pharmacol. Exp. Therap. (1985), 234, 395-401). The results obtained for particular compounds according to the present invention are as follows:

Compound	Chick retina Ki (nM)	Rabbit retina IC_{50} (nM)
Example 1	0.75	0.041
Example 3	0.16	0.022
Example 5	0.18	0.0031
Example 6	0.03	0.010
Example 11	0.02	0.029

CLAIMS

1. A compound of formula (I)



and pharmaceutically acceptable salts and solvates thereof,
wherein R^1 is a group of the formula $-CR^3R^4(CH_2)pNR^5COR^6$;
R^2 is hydrogen, halogen, C_{1-6}alkyl, OR^7 or CO_2R^7, and may be the same or different substituent when q is 2;
R^3, R^4 and R^5, which may be the same or different, are hydrogen or C_{1-6}alkyl;
R^6 is C_{1-6}alkyl or C_{3-7}cycloalkyl;
R^7 is hydrogen or C_{1-6}alkyl;
n is zero, 1 or 2;
p is an integer of 1, 2, 3 or 4;
q is 1 or 2; and
the dotted lines indicate the absence or presence of an additional bond.

2. A compound according to claim 1, wherein R^1 represents a group - $CR^3R^4(CH_2)_pNHCOR^6$,wherein R^3 and R^4 each independently represent hydrogen or C_{1-3} alkyl, p is an integer of 1 or 2, and R^6 is C_{1-3} alkyl or C_{3-5} cycloalkyl.

3. A compound according to claim 1 or 2, wherein R^3 and R^4 independently represent hydrogen.

4. A compound according to any of claims 1 to 3, wherein p is 1.

5. A compound according to any of claims 1 to 4, wherein R^2 is hydrogen, halogen or C_{1-3} alkyl.

6. A compound according to any of claims 1 to 5, wherein n is zero or 1.

7. N-(2-naphtho[2,1-b]furan-9-yl-ethyl)-acetamide;
N-[2-(1,2,6,7,8,9-hexahydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide;
N-[2-(4-fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide;
N-[2-(4-fluoro-1,2-dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide;
N-[2-(2,3-dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide;
N-[2-(3H-benzo[f]chromen-10-yl)-ethyl]-acetamide;
N-[2-(5-fluoro-2,3-dihydro-1H-benzo[f]chromen-10-yl)-ethyl]-acetamide;
Cyclopropanecarboxylic acid[2-(4-fluoro-naphtho[2,1-b]furan-9-yl)-ethyl]-amide;
N-[2-(5-Fluoro-3H-benzo[f]chromen-10-yl)-ethyl-acetamide;
and pharmaceutically acceptable salts and solvates thereof.

8. N-[2-(1,2-dihydro-naphtho[2,1-b]furan-9-yl)-ethyl]-acetamide, and pharmaceutically acceptable salts and solvates thereof.

9. A compound according to any of claims 1 to 8, for use in therapy.

10. A compound according to any of claims 1 to 8, for use in the preparation of a medicament for use in the treatment of conditions associated with a disturbed functioning of the melatonin system.

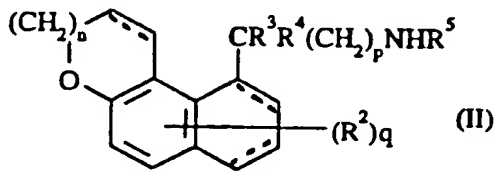
11. A method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound according to any of claims 1 to 8, for the treatment of conditions associated with a disturbed functioning of the melatonin system.

12. A pharmaceutical formulation comprising at least one compound according to any of claims 1 to 8, together with one or more pharmaceutically acceptable carriers therefor.

13. A process of preparing a pharmaceutical formulation, which process comprises mixing at least one compound of according to any of claims 1 to 8, together with one or more pharmaceutically acceptable carriers therefor.

14. A process of preparing a compound according to any of claims 1 to 8, which process comprises:

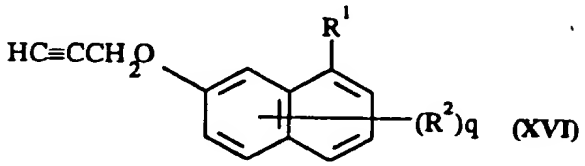
(a) acylation of a compound of formula (II)



(II)

or

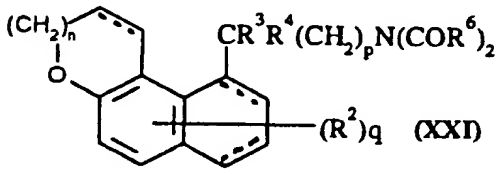
(b) cyclising a compound of formula (XVI)



(XVI)

or

(c) deacylation of a compound of formula (XXI)



(XXI)

15. Compounds of formula (II) to (VII), (XIV), (XV) and (XXI).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/01415

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/92 C07D311/92 A61K31/34 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 288 748 (THE UPJOHN COMPANY) 22 February 1994 see column 4, line 25 - column 4, line 32; claims 1-15 ---	1-15
A	DE,A,27 53 054 (CIBA-GEIGY AG) 8 June 1978 see page 3, line 18 - page 4, line 3; claims 1-6,16-19 ---	1-15
A	J. MED. CHEM., vol. 32, no. 9, 1989 pages 2128-2134, D. E. NICHOLS ET AL. 'Synthesis and Evaluation of N,N-Di-n-propyltetrahydrobenz(f)indol-7-amine and Related Congeners as Dopaminergic Agonists' * formulae 22, 23 * --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 1995	- 3. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Herz, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/01415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. MED. CHEM., vol. 37, no. 20, 1994 pages 3263-3273, P. STJERNLÖF ET AL. '6,7,8,9-Tetrahydro-N,N-di-n-propyl-3H-benzindol-8-amines. Derivatives as Potent and Orally Active Serotonin 5-HT(1A) Receptor Agonists' see tables 1-3 ---	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

ıational Application No
PCT/EP 95/01415

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	7175491	21-08-91
		EP-A-	0510068	28-10-92
		JP-T-	5503698	17-06-93
		WO-A-	9111435	08-08-91
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		AT-B-	361469	10-03-81
		AU-B-	517512	06-08-81
		AU-B-	3108777	07-06-79
		BE-A-	861337	30-05-78
		CA-A-	1097351	10-03-81
		FR-A,B	2372829	30-06-78
		GB-A-	1590648	03-06-81
		JP-A-	53068776	19-06-78
		NL-A-	7713241	05-06-78
		SE-A-	7713574	02-06-78
		US-A-	4171366	16-10-79